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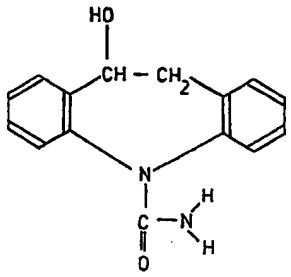
(19)

(54) NEW AZEPINE DERIVATIVE ITS PREPARATION AND COMPOSITION CONTAINING IT

(71) We, CIBA-GEIGY A.G., a Swiss company, of CH-4002, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new azepine derivative, to a process for its production, to medicaments containing the new compound and to their use.

An azepine derivative of the formula I,

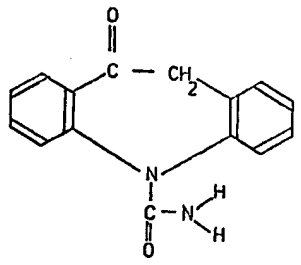


(I)

has not been known hitherto.

It has now been found that this compound, 10 - hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide, possesses valuable pharmacological properties and a particularly high therapeutic index. In the case of oral or rectal administration it has a central depressant action, as can be shown, e.g. in the observation test. Furthermore, it has an anticonvulsive action, relaxes the central muscular system and inhibits the fighting reaction of the mouse. These properties, which are determined by selected standard tests [cp. R. Domenjoz and W. Theobald, Arch. Int. Pharmacodyn. *120*, 450 (1959) and W. Theobald et al., Arzneimittel-Forsch. *17*, 561 (1967),] characterise the compound as being suitable for the treatment of psychosomatic disturbances, epilepsy, trigeminal neuralgia and cerebral spasticity.

The 10 hyrdoxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide, according to formula I, is produced by reducing 10 - oxo - 10,11 - dihydro - 5H - dibenz [b,f]azepine - 5 - carboxamide which corresponds to formula:



The reduction of a ketone to the corresponding hydroxy compound of the formula I can be performed with hydrogen in the presence of a catalyst, especially in the presence of copper chromite. The catalytic hydrogenation is preferably carried in a solvent. Suitable solvents are e.g. ethereal liquids such as dioxane, diethylene glycol dimethyl ether or diethylene glycol diethyl ether.

The starting material, 10 - oxo - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide, is produced, for example, starting with 10 - methoxy - 5H - dibenz [b,f]azepine (cp. J. R. Geigy A.G., Belgian Patent No. 597.793), as follows:

The stated enol ether is reacted with phosgene in toluene to form 10 - methoxy - 5H - dibenz[b,f]azepine - 5 - carbonyl - chloride, which, when reacted with ammonia in ethanol yields 10 - methoxy - 5H - dibenz [b,f]azepine - 5 - carboxamide; this enol ether is converted by boiling with dilute hydrochloric acid into the ketone.

As mentioned above, the new active substance is administered orally or rectally. The dosage depends on the manner of administration, the species, the age and on the individual condition. The daily dosage of the

active substance varies between 2.8 mg/kg and 8.5 mg/kg for warm-blooded animals. Suitable dosage units such as dragées, tablets or suppositories, preferably contain 30 to 200 mg of the active substance according to the invention.

Dosage units for oral administration contain, as active substance, between 10 and 90% of the compound of the formula I. They are produced by combining the active substance with, e.g. solid pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The dragée cores are coated, e.g. with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or in mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between varying dosages of active substance.

Other suitable dosage units for oral administration are hard gelatin capsules as well as soft closed capsules made from gelatine and a softener, such as glycerin. The hard capsules preferably contain the active substance as a granulate, e.g. in admixture with fillers such as maize starch, and/or lubricants such as talcum or magnesium stearate and, optionally, with stabilisers such as sodium metabisulphite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substances is preferably dissolved or suspended in suitable liquids such as liquid polyethylene glycols, whereby stabilisers can also be added.

Suitable dosage units for rectal administration are, e.g. suppositories consisting of a combination of the active substance with a suppository foundation substance. Suitable as a suppository foundation substance are, e.g. natural or synthetic triglycerides, paraffin hydrocarbons or polyethylene glycols. Also suitable are gelatine rectal capsules consisting of a combination of the active substances and a foundation substance. Suitable as a foundation substances are, e.g. liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

The following prescriptions further illustrate the production of tablets, dragées, capsules and suppositories:

a) 500.0 g of 10 - hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide are mixed with 550.0 g of lactose and 292.0 g of potato starch. The mixture is then moistened with an ethanolic solution of 8.0 g of gelatine, granulated through a sieve and dried. 60.0 g of potato starch, 60.0 g of talcum, 10.0 g of magnesium stearate and 20.0 g of highly dispersed silicon dioxide are mixed in and the mixture is pressed into 10,000 tablets each weighing 150 mg and each containing 50 mg of active substance. Optionally, the tablets can be provided with grooves for more precise adjustment of the dosage amount.

b) A granulate is produced from 1000 g of 10 - hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide, 379.0 g of lactose and an aqueous solution of 6.0 g of gelatine. After being dried, the granulate is mixed with 10.0 g of colloidal silicon dioxide, 40.0 g of talcum, 60.0 g of potato starch and 5.0 g of magnesium stearate and the mixture is pressed into 10,000 dragée cores. These are afterwards coated with a concentrated syrup made from 533.5 g of crystallised saccharose, 20.0 g of shellac, 75.0 g of gum arabic, 250.0 g of talcum, 20.0 g of colloidal silicon dioxide and 1.5 g of dyestuff, and then dried. The obtained dragées each weigh 240 mg and each contain 100 mg of active substance.

c) To produce 1000 capsules each containing 75 mg of active substance, 75.0 g of 10 - hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide are mixed with 198.0 g of lactose. The mixture is evenly moistened with an aqueous solution of 2.0 g of gelatine and is then granulated through a suitable sieve (e.g. sieve III according to Ph.Helv. V). The granulate is mixed with 10.0 g of dried maize starch and 15.0 g of talcum and the mixture is uniformly filled into 1000 hard gelatine capsules, size 1.

d) A suppository foundation mixture is prepared from 10.0 g of 10 - hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide and 158.5 g of adeps solidus and from this mixture are filled 100 suppositories each containing 100 mg of active substance.

The following Example illustrates the production of the new compound of the formula I and of starting materials not known hitherto, but the Example in no way limits the scope of the invention. The temperatures are given in degrees Centigrade.

Example

a) 30 g of 10 - oxo - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide are hydrogenated in 250 ml of abs. dioxane, with the addition of 5 g of copper chromite catalyst, with hydrogen at 100—110° and under 150 atmospheres in an autoclave for 6.5 hours until the absorption of hydrogen ceases. After completion of the reaction, the

catalyst is separated by filtration and the solvent distilled off under a water-jet vacuum. The residue is crystallised from ethanol to obtain 10 - hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide, M.P. 195—196°. Yield 23 g, 76% of the theoretical value.

The starting material, 10 - oxo - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide, is produced as follows:

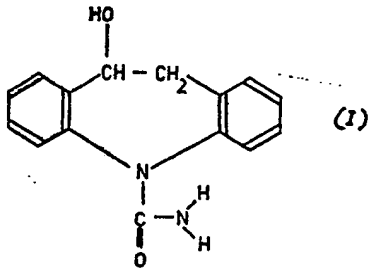
b) 223 g of 10 - methoxy - 5H - dibenz [b,f]azepine (c. J. R. Geigy A.G., Belgian Patent No. 597.793) are heated in 1500 ml of abs. toluene, whilst being stirred, to 30°. A vigorous stream of phosgene is then introduced into the reaction mixture. The internal temperature is raised in the course of 3 hours to 95° and the reaction mixture is then held for one hour at this temperature. The supply of phosgene is then interrupted, the source of heat removed and the excess of phosgene blown out with dry nitrogen. The precipitated reaction product is afterwards filtered off with suction. The filtrate is concentrated by evaporation under a water-jet vacuum and the residue crystallised from ethanol. A further amount of the reaction product is obtained which, together with the first fraction, is recrystallised from ethanol, whereupon the resulting 10 - methoxy - 5H - dibenz[b,f]azepine - 5 - carbonyl chloride melts at 138°. Yield 221 g, 77% of the theoretical value.

c) 215 g of the carbonyl chloride, produced according to b), are refluxed in 2000 ml of ethanol. Anhydrous ammonia is introduced for 4 hours, whilst stirring, into the boiling solution. The reaction mixture is subsequently cooled to room temperature and is then poured into 5000 ml of water. The precipitated crystals are filtered off with suction and washed with water. The moist crude product is recrystallised from ethanol, whereupon 10 - methoxy - 5H - dibenz [b,f] azepine - 5 - carboxamide, M.P. 181°, is obtained. Yield 148 g, 73% of the theoretical value.

d) 65 g of the carboxamide, obtained according to c), are refluxed with 650 ml of 2N hydrochloric acid for 2 hours. After cooling, the reaction product is filtered off with suction. After recrystallisation from ethanol, there is obtained the 10 - oxo - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide, M.P. 215—216°. Yield 49 g, 80% of the theoretical value.

WHAT WE CLAIM IS:—

1. 10 - Hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide corresponding to the formula:



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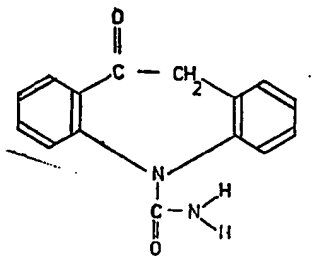
2. Process for the production of 10 - hydroxy - 10,11 - dihydro - 5H - dibenz [b,f]azepine - 5 - carboxamide which comprises reducing a ketone of the formula:



3. A therapeutic preparation which comprises 10 - hydroxy - 10,11 - dihydro - 5H - dibenz[b,f]azepine - 5 - carboxamide and an inert carrier.

4. A process as claimed in claim 2, substantially as hereinbefore described with reference to the foregoing Example.

5. A preparation as claimed in claim 3 substantially as hereinbefore described with reference to any of the foregoing prescriptions.

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